MATTERS ARISING

Relation between fractional urate excretion and serum triglyceride concentrations

A recent letter in the journal reported that after a dietary intervention 15 hyperuricaemic-hyperlipidaemic subjects showed considerably decreased triglyceride and cholesterol concentrations and increased renal excretion of uric acid.¹ This observation is of interest since patients with hyperlipidaemia often suffer from hyperuricaemia and vice versa.² Furthermore, evidence for an uricosuric effect of fenofibrate and for a lipid lowering effect of benzbromarone has been reported.³ Therefore, correlations between fractional urate excretion (calculated from urate and creatinine levels measured in serum and in morning untimed urine specimens⁴) and serum cholesterol and triglyceride concentrations have been studied in 4057 consecutive adult subjects (2010 women), under unrestricted diet, from Renzetti Hospital, Lanciano (Chieti, Italy). Fifty four per cent of the females and 49% of the males were outpatients.

Morning blood and urine samples were taken after an overnight fast. The biochemical tests were performed by an autoanalyser (Monarch, Instrumentation Laboratory) using standard methods. Only patients with a fasting blood glucose concentration less than or equal to 110 mg dl⁻¹ were considered since serum urate levels are significantly related to development of glucose intolerance⁵ and in diabetic subjects glycosuria can affect uric acid excretion.⁶ Using these selection conditions, the number of patients decreased to 3058 subjects.

The mean age values (SD) were 55.56 (17.03) years in men and 53.24 (17.13) years in women. Serum urate levels were higher in men than in women, at 5.54 (1.70) v 4.30 (1.63) mg dl⁻¹, while fractional urate excretion was higher in female subjects than in their male counterparts: 12.40 (9.97) % v 10.11 (13.41) %. The mean serum triglyceride concentration was 141.55 (113.26) mg dl⁻¹ in men and 121.39 (93.26) mg dl⁻¹ in women. As shown in the table, in both sexes serum triglyceride concentration was inversely correlated with fractional urate excretion as obtained by simple and multiple linear regression analyses performed using age, serum cholesterol, and serum triglyceride as predictors of fractional urate excretion (dependent variable). The association was highly significant (P < 0.001).

Table 1 Association between fractional urate excretion and age, serum cholesterol, triglyceride levels in 1511 men and in 1547 women as determined by simple and multiple linear regression analysis

		Age	Serum cholesterol	Serum triglyceride
Simple linear regression analysis	Men	0.102***	-0.067**	-0.119***
	Women	-0.083**	0.017(NS)	-0.092***
Multiple linear regression analysis	Men	0.095***	-0.011(NS)	-0.118***
	Women	-0.069**	0.068*	-0.106***

Results are standardised β coefficient and significance.

All variables were normalised by logarithmic transformation except age.

Significance level: *** P < 0.001; ** P < 0.01; * P < 0.05; (NS) P > 0.05.

Acute elevation of serum triglyceride did not modify uric acid excretion or serum urate levels in previous studies.^{7,8} However, these data are not conclusive since infused triglycerides have a different composition and metabolic origin from endogenous triglycerides. In addition prolonged elevation might have effects not elicited from these acute experiments. Regardless of the mechanism—perhaps involving structural components of very low density lipoproteins⁹—the present data from a large cross sectional study show an inverse relation between renal excretion of uric acid and serum triglyceride concentration.

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Should patients with recent onset of rheumatoid arthritis be offered genetic screening?

We would like to compliment Dr Symmons and her colleagues on their paper in the journal,¹ which reviews the evidence for the role of genetic factors in the progression of rheumatoid disease. A slight area for disagreement would be that the authors suggest that we have used genetic factors to screen patients for early rheumatoid arthritis. The term "screening" is normally applied to populations at risk of disease, whereas the

suggestion we have made is that genetic factors may be of use as one of the several factors that are capable of aiding in the prediction of poor prognosis. Thus we use it as part of the second stage of a two stage process. Patients who have already fulfilled stage 1 have developed the markers of persistence, that is, symmetrical small joint arthritis of a certain duration.

Genetic factors have the particular advantages that they are present from onset (which will become increasingly important the earlier patients are studied) and are unchanged by treatment. In our previous prospective study of patients fulfilling ACR criteria,² testing this hypothesis we showed a 13-fold relative risk for possession of rheumatoid factor or the shared epitope. This is clearly of predictive value. Furthermore, with radical new treatments which may profoundly alter the outcome of rheumatoid arthritis, it produces information on what might have happened if the natural course of the disease had been followed, for example it is known that most hospital based populations of patients with rheumatoid arthritis possess rheumatoid factor in around 70% of cases and have a shared epitope in 70-80%, which rises to over 90% in those with severe disease. A major deviation from this frequency would suggest that milder patients are being treated. Several longitudinal studies of patients who have been tissue typed are now being analysed, and these should provide good information on the relation between genetic factors and outcome in clinical practice.

We wholeheartedly agree with the final suggestion that establishing well designed clinical outcome studies of rheumatoid arthritis stratified by HLA DRB1 genotypes would be of value. We have already done this in Yorkshire from a population of several million where for the last 18 months new patients with inflammatory arthritis have been routinely tissue typed. Controlled intervention studies based on this information are nearing the completion of recruitment, and data should soon be available. Until that time it is inappropriate to use tissue typing other than as an adjunct to clinical diagnosis. We would certainly agree that at present it is not justifiable to use this outside major research centres.

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Authors' reply

We would like to thank Professor Emery and his colleagues for their interest in our paper. The purpose of the paper was to review the current published evidence that screening of patients with recent onset rheumatoid arthritis for the shared epitope or other genetic markers could be used to guide treatment decisions. All the papers which we included had examined the prognostic value of genetic markers in patients who satisfied classification criteria for rheumatoid arthritis.

We did not suggest that any of the authors had substituted genetic screening for the classification criteria.

As shown in our paper, patients who have one or more copies of the shared epitope do have a worse prognosis. However, those who are shared epitope negative do not universally have a good prognosis. Between 19% and 30% develop radiological erosions. One could not, therefore, advocate withholding potential disease modifying agents from this group.

We are delighted that Professor Emery and his group are examining the value of stratification by HLA-DRB1 genotype in a controlled clinical trial. We look forward to the publication of the results of these studies. In the meantime we are all agreed that testing for the possession of the shared epitope should remain a research tool and should not become part of routine clinical practice.

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LETTERS TO THE EDITOR

Serum and synovial fluid levels of interleukin-5 in a patient with eosinophilic fasciitis

Eosinophilic fasciitis was initially described by Shulman¹ as a syndrome involving skin lesions, oedema of the extremities, polyarthralgia, eosinophilia, an elevated erythrocyte sedimentation rate (ESR), and hypergammaglobulinaemia. Its aetiology is not well understood. An increase in circulating immune complex levels was reported as one possibility.² Interleukin-5 (IL-5), a T cell replacing factor, induces eosinophilia in the blood and the production of autoantibodies.^{3,4} We investigated the role of IL-5 in a patient with eosinophilic fasciitis.

A 31 year old Japanese woman, a nurse, developed swelling, stiffness, and pain in both hands, elbows, and knees on November 10, 1995. She had not performed any vigorous exercise or physical work before the onset of symptoms. She was initially treated with a non-steroidal anti-inflammatory drug (NSAID), prescribed by a local orthopaedic specialist. However, on November 20 she developed a low grade fever and oedema of both hands, upper arms, and (mainly) the lower legs. She was then admitted to our hospital for detailed examination and treatment. Evaluation of the peripheral blood showed marked eosinophilia (31%, 4061 μl^{-1}) and mild leucocytosis (13 100 μl^{-1}), but no anaemia (RBC $451 \times 10^4 \mu\text{l}^{-1}$, Hb 13.1 g dl^{-1}). Serological testing was negative for antinuclear antibody, rheumatoid factor, antithyroglobulin antibody, and antimicrobial antibody. The serum level of complements, immunoglobulins, and the proportions of the lymphocyte subpopulation and the CD4/8 ratio were all normal, as were blood chemistry findings. The erythrocyte

Micrograph showing the perivascular infiltration of mononuclear cells and eosinophils in the fascia. (Haematoxylin and eosin staining, $\times 354$.)

sedimentation rate was raised (21 mm h was present) and positivity for serum CRP was present (2.2 mg ml^{-1}). Serum iron was 16 $\mu\text{g dl}^{-1}$, and the total iron binding capacity was 226 $\mu\text{g dl}^{-1}$. Radiographs of the chest, hand, and knee showed no abnormalities or erosive lesions. The clinical and laboratory findings suggested a diagnosis of eosinophilic fasciitis. As confirmation, we obtained an en bloc surgical biopsy specimen extending from the skin through the muscle of left lower leg. Histological evaluation showed hyperkeratosis of the epidermis, with fibrosis and infiltration of lymphocytes and eosinophilic leucocytes around the small vessels in the dermis. Granulomas were found in the subcutaneous tissue, consisting of epithelial cells, macrophages, and multinucleated giant cells surrounded by eosinophilic leucocytes. The adipose tissue and fascia showed similar histological findings, that is, granulomas and infiltration of eosinophilic leucocytes (figure). The muscle was unaffected. Pathological findings were compatible with a diagnosis of eosinophilic fasciitis, according to the findings of Barnes *et al.*⁵ Because of bilateral swelling of the knee joints, the left knee joint was aspirated to sample the synovial fluid. Ten millilitres of fluid were obtained. It was straw coloured and turbid. The mucin clot was fair and crystals were absent. The white blood cell count in the synovial fluid was 1646 μl^{-1} , with lymphocytes 75%, monocytes 21%, neutrophils 2%, and eosinophils 2%. The patient was not receiving steroids. These findings were also compatible with eosinophilic fasciitis.⁶

Concentrations of IL-5 were measured in the serum and synovial fluid using an ELISA kit (R&D Systems Inc, Minneapolis, MN, USA). IL-5 concentrations in sera were not detectable (less than 8 pg ml^{-1}) before or after steroid treatment, but the level of IL-5 in synovial fluid was 32 pg ml^{-1} before therapy. No synovial fluid was obtained after therapy. As controls, the levels of IL-5 in SF from three patients with rheumatoid arthritis and three patients with osteoarthritis were measured and were undetectable.

Treatment was initiated with prednisolone, 40 mg per day, and symptoms such as fever, oedema, polyarthralgia, and eosinophilia disappeared within a week. The dose was gradually tapered. The patient is presently in remission.

To our knowledge, concentrations of IL-5 in serum or synovial fluid have not previously been measured in eosinophilic fasciitis. The IL-5 level in synovial fluid from our patient (32 pg ml^{-1}) was lower than that in serum previously reported in a patient with the pulmonary infiltration with eosinophilia (PIE) syndrome (53 pg ml^{-1}).⁷ This IL-5 concentration in synovial fluid was higher than in synovial fluid from patients with rheumatoid arthritis or osteoarthritis. There was, however, no striking infiltration of eosinophils in the joint (2%). The possibilities to explain this result are as follows: (1) the effect of human IL-5 on eosinophils is chemokinetic rather than chemotactic *in vitro* (⁸ and Hirashima M, personal communication); (2) the amount of IL-5 detected (32 pg ml^{-1}) may be not sufficient to induce the massive eosinophil infiltration; (3) IL-5 produced in joint space might not be released into circulation, remaining in joint. Recently, Kopf *et al.*⁹ reported that basal levels of eosinophils with normal morphology were produced even in IL-5 deficient mice. They suggested the involvement of IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF) in the development of eosinophils as well as IL-5. The expression of the gene for IL-3 was reportedly activated in a patient with acute lymphocytic leukaemia with eosinophilia.¹⁰ Thus IL-3 or GM-CSF, in addition to IL-5, may also be engaged in the induction of eosinophilia in patients with eosinophilic fasciitis.

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